



United States Patent [19]

Young et al.

[11] Patent Number: 6,048,850

[45] Date of Patent: Apr. 11, 2000

[54] **METHOD OF INHIBITING
PROSTAGLANDIN SYNTHESIS IN A HUMAN
HOST**

[76] Inventors: **Donald A. Young**, 540 Clover Hills Dr., Rochester, N.Y. 14618; **Michael K. O'Banion**, 3613 Clover St., Pittsford, N.Y. 14534; **Virginia D. Winn**, 139 Raleigh St., Rochester, N.Y. 14620

[21] Appl. No.: 08/487,744

[22] Filed: Jun. 7, 1995

Related U.S. Application Data

[60] Division of application No. 08/487,752, Jun. 7, 1995, and a continuation-in-part of application No. 08/034,143, Mar. 22, 1993, abandoned, which is a continuation of application No. 07/949,780, Sep. 22, 1992, abandoned, said application No. 08/487,752, is a continuation-in-part of application No. 08/231,456, Apr. 20, 1994, abandoned, which is a continuation-in-part of application No. 08/054,364, Apr. 28, 1993, abandoned, which is a continuation-in-part of application No. 07/983,835, Dec. 1, 1992, abandoned, which is a continuation-in-part of application No. 07/949,780.

[51] **Int. Cl.**⁷ **A61K 31/33**; A61K 31/18; A61K 31/53; C12Q 1/26

[52] **U.S. Cl.** **514/183**; 514/1; 514/241; 514/326; 514/601; 435/25; 435/28; 435/29; 435/183; 435/189

[58] **Field of Search** 514/44, 1, 825; 514/886, 885, 183, 605, 601; 536/24.5; 935/34, 36; 435/25, 29, 28, 189, 183

[56] References Cited

U.S. PATENT DOCUMENTS

4,950,599 8/1990 Bertling 435/172.3
4,980,281 12/1990 Housey 435/29
5,087,572 2/1992 Castellino et al. 435/240.2

OTHER PUBLICATIONS

DeWitt et al., 1993, "PGH Synthase isoenzyme selectivity: The potential for safer nonsteroidal antiinflammatory drugs", *Am J Med* 95(2a):40S-44S.

DeWitt et al., 1990, "The aspirin and heme-binding sites of ovine and murine prostaglandin endoperoxide synthases", *J Biol Chem* 265:5192-5198.

Dickson et al., 1993, "Microglia and cytokines in neurological disease, with special reference to AIDS and Alzheimer's disease", *Glia* 7:75-83.

Espey, 1980, "Ovulation as an inflammatory reaction—A hypothesis", *Biol Reproduct* 22:73-106.

Espey, 1982, "Optimum time for administration of indomethacin to inhibit ovulation in the rabbit", *Prostaglandin* 23:329-335.

Funk et al., 1991, "Human platelet/erythroleukemia cell prostaglandin G/H synthase: cDNA cloning, expression and gene chromosomal assignment", *FASEB J* 5:2304-2312.

Futaki et al., 1992, "Selective inhibition of NS-398 on prostanoic production in inflamed tissue in rat carrageenan-air-pouch inflammation", *J Pharm Pharmacol* 45:753-755.

Griffin et al., 1989, "Brain interleukin 1 and S-100 immunoreactivity are elevated in Down syndrome and Alzheimer disease", *Proc Natl Acad Sci* 88:7611-7615.

Han et al., 1990, "Persistent induction of cyclooxygenase in p60^{src}-transformed 3T3 fibroblasts", *Proc Natl Acad Sci* 87:3373-3377.

Herschmann et al., 1992, "Characterization of a gene encoding a second prostaglandin synthase/cyclooxygenase (PGS/COX), whose message and protein are induced by mitogens and inhibited by glucocorticoids", *8th International Conference on Prostaglandins and Related Compounds* on Jul. 26-31, 1992, Montreal, Canada, Abstract 302.

Herschmann, 1994, "Regulation of prostaglandin synthase-1 and prostaglandin synthase-2", *Cancer and Metastasis Reviews* 13:241-256.

Hla & Neilson, 1992, "Human cyclooxygenase-2 cDNA", *Proc Natl Acad Sci* 89:7384-7388.

Hla et al., 1986, "Isolation of the cDNA for human prostaglandin H synthase", *Prostaglandins* 32:829-845.

Johnson et al., 1992, "Complement mRNA in the mammalian brain: Responses to Alzheimer's disease and experimental brain lesioning", *Neurobiol Aging* 13:641-648.

Jones et al., 1993, "Molecular cloning of human prostaglandin endoperoxide synthase type II and demonstration of expression in response to cytokines", *J Biol Chem* 268:9049-9054.

Kelly, 1994, "Pregnancy maintenance and parturition: The role of prostaglandin in manipulating the immune and inflammatory response", *Endocrine Reviews* 15(5):684-706.

Kimura and Ikeda-Saito, 1988, "Human myeloperoxidase and thyroid peroxidase, two enzymes with separate and distinct physiological functions, are evolutionary related members of the same gene family", *Prot Struct Func Genet* 3:113-120.

Kitzler et al., 1992, "Two distinct forms of prostaglandin H synthase (PHS) are induced in rat tracheal epithelium cells by TPA and EGF treatment", *8th International Conference on Prostaglandins and Related Compounds* on Jul. 26-31, 1992, Montreal, Canada, Abstract 528.

Kujubu et al., 1991, "TIS10, a phorbol ester tumor promoter-inducible mRNA from Swiss 3T3 cells, encodes a novel prostaglandin synthase/cyclooxygenase homologue", *J Biol Chem* 266:12866-12872.

(List continued on next page.)

Primary Examiner—Carla J. Myers

Attorney, Agent, or Firm—Pennie & Edmonds LLP

[57]

ABSTRACT

The invention relates to the gene encoding the mammalian prostaglandin H synthase-2 and its product. More specifically, the invention relates to the diagnosis of aberrant PGHS-2 gene or gene product; the identification, production, and use of compounds which modulate PGHS-2 gene expression or the activity of the PGHS-2 gene product including but not limited to nucleic acid encoding PGHS-12 and homologues, analogues, and deletions thereof, as well as antisense, ribozyme, triple helix, antibody, and polypeptide molecules as well as small inorganic molecules; and pharmaceutical formulations and routes of administration for such compounds.

8 Claims, 22 Drawing Sheets